Rejection of Claims 1, 8-11, 13, 14, 34-40 and 53

Claim 1 relates to a method of treating sitosterolemia, comprising administering to a mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or prodrug of the at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or mixture thereof.

Claim 1 does not require combination with another drug.

Claims 8-11 depend from claim 1 and recite more specific groups of sterol absorption inhibitors. Claims 13 and 14 also depend from claim 1 and recite amounts of sterol absorption inhibitor to be administered.

Claims 34-40 and 53 relate to methods of reducing plasma or tissue concentration of at least one non-cholesterol sterol, 5-α stanol, or mixture thereof by administering such compounds, including to sitosterolemics.

Rosenblum et al. disclose that ezetimibe, optionally in combination with an HMG-CoA reductase inhibitor such as simvastatin or lovastatin, is useful for reducing cholesterol and risk of atherosclerosis. As acknowledged in the Final Office Action at page 4, lines 3-5, *Rosenblum et al. do not suggest or disclose use of ezetimibe, alone or in combination with an HMG-CoA reductase inhibitor or cholestyramine, for treating sitosterolemia* (emphasis added).

Belamarich et al. do not suggest or disclose that ezetimibe or other sterol absorption inhibitors are useful for treating sitosterolemia. Belamarich et al. do not suggest or disclose that HMG-CoA reductase inhibitors are useful for treating sitosterolemia. Belamarich discloses treatment of a sitosterolemic patient with cholestyramine. See Belamarich et al. Abstract. Belamarich et al. do not teach that hypercholesterolemia is "one of the manifestation[s] of sitosterolemia" as alleged in the Final Office Action, but rather that some sitosterolemics also can have hypercholesterolemia.

In the "Response to Arguments" section of the Final Office Action, it is alleged that:

> Hidaka et al. teaches an HMG-CoA reductase inhibitor as effective in treating sitosterolemia [in] that it can reduce the plant sterol level in sitosterolemic patients. Therefore, employing HMG-CoA reductase inhibitor in a method of treating sitosterolemia along with other agents such as those herein claimed would be reasonably expected to be successful and effective.

Applicant respectfully disagrees with this characterization of the teachings of Hidaka et al. and respectfully requests that the reference be reviewed again.

In the Hidaka et al. study, the effects of cholestyramine and pravastatin were only evaluated on a single sitosterolemic patient. See Hidaka et al. at page 61, col. 2, lines 8-10. The other patients treated were hypercholesterolemic, *not sitosterolemic*. See Hidaka et al. at page 61, col. 1, line 14 – col. 2, line 7.

Hidaka et al. stated that "[t]he plasma of the [sitosterolemic] patient contained large amounts of plants sterols as well as cholestanol. ***The patient had been treated with cholestyramine, but unfortunately could not tolerate the treatment because of her associated hemorrhoids***. The patient was treated with probucol and pravastatin with her informed consent." See Hidaka et al. at page 61, col. 2, lines 15-20 (emphasis added).

Hidaka et al. further stated "The patient with sitosterolemia ***who could not tolerate cholestyramine*** treatment underwent treatment with other drugs for more than 3 years....***Pravastatin*** (10-20 mg/day) ***administration had little effect on plasma sterol concentrations*** when data from 1991...were used for evaluation ...**sitosterol, 31.8 ± 4.34, 31.0 ± 1.91**" during the treatment with pravastatin. See Hidaka et al. at page 61, col. 2, lines 24-30 (emphasis added).

Hidaka et al. stated that "***Pravastatin had little effect on plasma sterol levels in a sitosterolemic patient***" and "[t]he ***ineffectiveness of an HMG-CoA reductase inhibitor in lowering plasma sterol concentrations in our sitosterolemic patient as well as in the subjects reported by Nguyen et al....is also difficult to explain***." See Hidaka et al. at page 64, col. 1, lines 43-44

and lines 13-16, respectively (emphasis added). Also, Hidaka et al. disclose that "**Nguyen et al....reported that plasma sterol levels were not lowered by an HMG-CoA reductase inhibitor, lovastatin, in sitosterolemic patients. Our results in a patient with this rare disease mostly agree with theirs.**" See Hidaka et al. at page 63, col. 2, lines 16-19, (emphasis added).

Hidaka et al. clearly do **not** teach that an HMG-CoA reductase inhibitor is effective in treating sitosterolemia [in] that it can reduce the plant sterol level in sitosterolemic patients, as alleged in the Final Office Action. Applicant respectfully requests review of the Hidaka et al. reference and correction of this misstatement in the file record.

The conclusion that "employing an HMG-CoA reductase inhibitor in a method of treating sitosterolemia along with other agents such as those herein claimed would be reasonably expected to be successful and effective" is based upon a misinterpretation of the teachings of the Hidaka et al. reference and therefore the prima facie case of obviousness is not properly supported and must be withdrawn.

Clearly, the teachings of Hidaka et al. and others illustrate that compounds that are used to treat hypercholesterolemia (such as pravastatin or lovastatin) may not be effective in treating sitosterolemia. Hidaka et al. clearly discloses that pravastatin was not effective in treating a sitosterolemic patient. Also, Hidaka et al. disclose that "Nguyen et al....reported that plasma sterol levels were not lowered by an HMG-CoA reductase inhibitor, lovastatin, in sitosterolemic patients."

According to L. Nguyen et al., "Regulation of Cholesterol Biosynthesis in Sitosterolemia: Effects of Lovastatin, Cholestyramine, and Dietary Sterol Restriction", 32 J. Lipid Res. (1991) 1941-1948, 1946, "lovastatin, which is a potent competitive inhibitor of HMG-CoA reductase...did not reduce plasma cholesterol and plant sterols in homozygous sitosterolemic patients".

As a further example, "[l]ovastatin, a competitive inhibitor of cholesterol biosynthesis that is widely used in the treatment of hypercholesterolemia has

been tried but has not been an effective treatment in sitosterolemia." G. Salen et al., 33 Journal of Lipid Research 945-955, 952 (1992).

Based upon the foregoing teachings, it would not be obvious to one skilled in the art to administer a compound useful for treating hypercholesterolemia to a sitosterolemic patient because of the lack of success as shown above.

In the "Response to Arguments" section of the Final Office Action, it is stated that Applicant's arguments with regard to long-felt need were considered but not found to be persuasive because there was allegedly no showing that others of ordinary skill in the art were working on the problem and, if so, for how long and that there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. Final Office Action at page 5, lines 13-19.

Clearly, the Hidaka et al. and Nguyen et al. references discussed above show that those of ordinary skill in the art were working on the problem of treating sitosterolemia without the deleterious side effects associated with cholestyramine.

Hidaka et al. disclose that treatment of a sitosterolemic patient with cholestyramine was unsuccessful because the patient could not tolerate the treatment because of her associated hemorrhoids. See Hidaka et al. at page 61, col. 2, lines 24-30. Hidaka et al. also discloses that pravastatin had little effect on plasma sterol levels in a sitosterolemic patient. Id. Nguyen et al. disclose that lovastatin was not effective in treating sitosterolemia. See Nguyen et al. at 1946.

Regarding others working on the problem, Hidaka et al. disclose that "Miettinen at al....recently reported that...plasma plant sterol levels tended to be increased during combined treatment with lovastatin and cholestyramine." See Hidaka et al. at page 63, col. 2, lines 8-12. Further, Hidaka et al. disclose that "Nguyen et al....reported that plasma sterol levels were not lowered by an HMG-CoA reductase inhibitor, lovastatin, in sitosterolemic patients. Our results in a

patient with this rare disease mostly agree with theirs." See Hidaka et al. at page 63, col. 2, lines 16-19.

The Miettinen references cited by Hidaka et al. were published in 1992 and 1991. The Nguyen et al. references cited by Hidaka et al. were published in 1990 and 1991. The Hidaka et al. reference was published in 1995. The Hidaka et al. reference shows the undesirability of cholestyramine as a treatment for sitosterolemia, that the need for alternative treatments has been a persistent one over a number of years that was recognized by those of ordinary skill in the art, and provides evidence of prior unsuccessful attempts to solve the problem using lovastatin and pravastatin. See M.P.E.P § 716.04.

This long-felt need has not been adequately satisfied by another. R. Steiner et al., "Sitosterolemia", http://www.emedicine.com/ped/topic2110.htm (April 5, 2005) (submitted with the Information Disclosure Statement filed concurrently herewith) discloses at page 8 that treatment may include dietary changes, pharmacologic agents, and/or surgical intervention. A diet low in plant sterols may be recommended. Bile acid-binding resins may be administered. An ileal bypass may be indicated. At page 9, Steiner et al. disclose that "bile acid-binding resins (e.g., cholestyramine, colestipol) or competitive inhibitory agents (e.g., sitostanol) could be considered."

According to R. Steiner et al. at page 9, "[i]n October 2002, a new cholesterol absorption inhibitor, ezetimibe, received US Food and Drug Administration (FDA) approval for use in sitosterolemia. Because the mechanism by which it inhibits cholesterol absorption is quite specific, the adverse effects and drug interactions associated with the resins should not be expected. A multiple center collaborative randomized placebo-controlled study of ezetimibe 10 mg/d in patients aged 10 years and older determined that ezetimibe was well tolerated and efficacious in reducing plant sterol levels compared with a placebo (Salen, 2004). Limited studies have been conducted on sitostanol in this context. Information on the use of medications other than cholestyramine (and,

more recently, ezetimibe) in sitosterolemia is limited; therefore, colestipol and sitostanol cannot generally be recommended."

Thus Hidaka et al. and others have recognized the undesirability of conventional treatments for sitosterolemia, such as cholestyramine. Hidaka et al. and Nguyen et al. disclose unsuccessful attempts to treat sitosterolemia using conventional cholesterol treatments such as pravastatin and lovastatin. R. Steiner et al. disclose that this long-felt need has been successfully satisfied by Zetia® ezetimibe formulation (which contains a compound of Formula (VIII) according to the presently claimed invention), which is approved by the US FDA for treatment of homozygous sitosterolemia. This treatment avoids the undesirable side effects such as constipation that can occur in sitosterolemic patients taking cholestyramine and avoids the pain and inconvenience of ileal bypass surgery, which are current standard treatments for sitosterolemia.

Sitosterolemia or phytosterolemia is an inherited disorder in which there is a hyperabsorption of phytosterols (plant sterols such as sitosterol, campesterol, stigmasterol and avenosterol) and shellfish sterols resulting in tendon and tuberous xanthomata. Stedman's Medical Dictionary, 27th Ed. (2000) 1381. Sitosterolemia also can result in accelerated atherosclerosis, hemolytic episodes, arthritis and arthralgias. G. Salen et al. at 945.

Plasma cholesterol concentrations can vary considerably in sitosterolemic subjects. Id. at page 946. As shown in Table 1 of the Salen reference, cholesterol levels in sitosterolemics may be low but are usually increased over age matched controls. Id. One homozygous sitosterolemic patient (subject CL) in Table 1 had a cholesterol level of only 134 mg/dl.

Applicant has shown that there is a long felt unfulfilled need for a treatment for sitosterolemics that inhibits absorption of phytosterols and shellfish sterols without the disadvantages of such treatments as cholestyramine (a bile acid sequestrant) or ileal bypass surgery. Assignee is successfully marketing Zetia® ezetimibe formulation in the United States for treatment of sitosterolemia.

Neither the teachings of Rosenblum et al. nor those of Belamarich et al., taken alone or combined as set forth in the Office Action, suggest or disclose use of a sterol or 5-α stanol absorption inhibitor, such as ezetimibe, for treatment of sitosterolemia. The Hidaka et al. and Nguyen et al. references disclose that others have recognized the long-felt need and unsuccessfully attempted to solve the problem using pravastatin and lovastatin (HMG-CoA reductase inhibitors). As discussed above, not all cholesterol treatments are successful for treating sitosterolemia. Neither Rosenblum et al. nor Belamarich et al. provides any guidance as to factors to predict success of cholesterol treatments for treating sitosterolemia. Applicant has shown a long-felt unfulfilled need for a treatment for sitosterolemia with less likelihood of deleterious side effects such as those associated with treatment with cholestyramine. Applicant's invention has successfully met this need, as discussed in detail above.

Therefore, Applicant respectfully requests that the rejection of claims 1, 8-11, 13, 14, 34-40 and 53 under 35 U.S.C. § 103 be reconsidered and withdrawn.

Rejection of claims 15-24, 33, 41, 42, 43, 54 and 55

Generally, claims 15-24, 33, 41, 42, 43, 54 and 55 depend from claims 1 and 39 and further require the presence of at least one lipid lowering agent, such as an HMG-CoA reductase inhibitor (for example simvastatin or lovastatin) with the at least one sterol absorption inhibitor.

As discussed above, Rosenblum et al. disclose that ezetimibe, optionally in combination with an HMG-CoA reductase inhibitor such as simvastatin or lovastatin, is useful for reducing cholesterol and risk of atherosclerosis. As acknowledged in the Final Office Action at page page 4, lines 3-5, *Rosenblum et al. do not suggest or disclose use of ezetimibe, alone or in combination with an HMG-CoA reductase inhibitor or cholestyramine, for treating sitosterolemia* (emphasis added).

Belamarich et al. do not suggest or disclose that ezetimibe or other sterol absorption inhibitors are useful for treating sitosterolemia. Belamarich et al. do

not suggest or disclose that HMG-CoA reductase inhibitors are useful for treating sitosterolemia. Belamarich discloses treatment of a sitosterolemic patient with cholestyramine. See Belamarich et al. Abstract. Belamarich et al. do not teach that hypercholesterolemia is "one of the manifestation[s] of sitosterolemia" as alleged in the Final Office Action, but rather that some sitosterolemics can also have hypercholesterolemia. Belamarich et al. teach away from using an HMG-CoA reductase inhibitor for treating sitosterolemia by noting '[I]t has recently been hypothesized that the hyperabsorption of plant sterols and cholesterol observed in sitosterolemia is a compensatory response to a deficiency of the rate-limiting enzyme of cholesterol biosynthesis, hydroxymethylglutaryl-Co A reductase". One skilled in the art would not be motivated by this disclosure in Belamarich et al. to administer an HMG-Co A reductase inhibitor to a sitosterolemic patient.

Hidaka et al. clearly do not teach that an HMG-CoA reductase inhibitor is effective in treating sitosterolemia [in] that it can reduce the plant sterol level in sitosterolemic patients, as alleged in the Final Office Action. Applicant respectfully requests that the Hidaka et al. reference be reviewed and this misstatement in the file record be corrected.

The conclusion that "employing an HMG-CoA reductase inhibitor in a method of treating sitosterolemia along with other agents such as those herein claimed would be reasonably expected to be successful and effective" is based upon a misinterpretation of the teachings of the Hidaka et al. reference and therefore the prima facie case of obviousness is not properly supported and must be withdrawn.

Clearly, the teachings of Hidaka et al. and others illustrate that compounds that are used to treat hypercholesterolemia (such as pravastatin or lovastatin) may not be effective in treating sitosterolemia. Hidaka et al. clearly discloses that pravastatin was not effective in treating a sitosterolemic patient. Also, Hidaka et al. disclose that "Nguyen et al....reported that plasma sterol levels were not lowered by an HMG-CoA reductase inhibitor, lovastatin, in sitosterolemic

patients." As a further example, "[l]ovastatin, a competitive inhibitor of cholesterol biosynthesis that is widely used in the treatment of hypercholesterolemia has been tried but has not been an effective treatment in sitosterolemia." G. Salen et al., 33 Journal of Lipid Research 945-955, 952 (1992). Therefore, it would not be obvious to one skilled in the art to administer a compound useful for treating hypercholesterolemia to a sitosterolemic patient.

Neither the teachings of Rosenblum et al. nor those of Belamarich et al., taken alone or combined as set forth in the Office Action, suggest or disclose use of a sterol or 5-α stanol absorption inhibitor, such as ezetimibe, in combination with an HMG-Co A reductase inhibitor for treatment of sitosterolemia. Hidaka et al. shows that pravastatin was not effective in treating sitosterolemia and thus provides no motivation for such a combination. As discussed above, not all cholesterol treatments are successful for treating sitosterolemia. Applicant has shown above a long-felt unfulfilled need for a treatment for sitosterolemia with less likelihood of deleterious side effects such as those associated with cholestyramine treatment. Applicant's invention has successfully met this need, as discussed in detail above.

Therefore, Applicant respectfully requests that the rejection of claims 15-24, 32, 33, 41, 42, 54 and 55 under 35 U.S.C. § 103 be reconsidered and withdrawn.

Rejection of claims 32 and 43-45

Generally, claims 32 and 43-45 relate to methods of treating sitosterolemia using at least one bile acid sequestrant with at least one sterol absorption inhibitor.

As discussed above, Rosenblum et al. disclose that ezetimibe, optionally in combination with an HMG-CoA reductase inhibitor such as simvastatin or lovastatin, is useful for reducing cholesterol and risk of atherosclerosis. As acknowledged in the Final Office Action at page page 4, lines 3-5, *Rosenblum et al. do not suggest or disclose use of ezetimibe, alone or in combination with an*

HMG-CoA reductase inhibitor or cholestyramine, for treating sitosterolemia (emphasis added). Rosenblum et al. do not suggest or disclose use of bile acid sequestrants at all.

Belamarich et al. do not disclose that ezetimibe or other sterol absorption inhibitors are useful for treating sitosterolemia. Belamarich discloses treatment of a sitosterolemic patient with cholestyramine. See Belamarich et al. Abstract. Belamarich et al. do not teach that hypercholesterolemia is "one of the manifestation[s] of sitosterolemia" as alleged in the Final Office Action, but rather that some sitosterolemics can also have hypercholesterolemia. Therefore, it would not be obvious to one skilled in the art to administer a sterol absorption inhibitor compound useful for treating hypercholesterolemia to a sitosterolemic patient.

Hidaka et al. discloses that cholestyramine treatment of a patient was discontinued due to an adverse side effect. Hidaka et al. do not suggest or disclose treatment of sitosterolemia with a sterol absorption inhibitor compound. Hidaka et al. disclose unsuccessful attempts to treat sitoterolemia with other cholesterol treatments, namely pravastatin and lovastatin. Thus, Hidaka et al. provide no motivation for treating a sitosterolemic patient with a sterol absorption inhibitor compound and bile acid sequestrant.

Neither the teachings of Rosenblum et al. nor those of Belamarich et al., taken alone or combined as set forth in the Office Action with Hidaka et al., suggest or disclose use of a sterol or 5-α stanol absorption inhibitor, such as ezetimibe, in combination with a bile acid sequestrant for treatment of sitosterolemia. As discussed above, not all cholesterol treatments are successful for treating sitosterolemia. Applicant has shown above a long-felt unfulfilled need for a treatment for sitosterolemia. Applicant's invention has successfully met this need, as discussed in detail above.

Therefore, Applicant respectfully requests that the rejection of claims 32 and 43-45 under 35 U.S.C. § 103 be reconsidered and withdrawn.

In view of the foregoing remarks, it is respectfully submitted that all of the pending claims in the present application are distinguishable from the cited prior art. Accordingly, reconsideration and withdrawal of the rejection and an early Notice of Allowance are respectfully requested.

Respectfully submitted,
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Dated: April 8, 2005

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